REMARKS

Reconsideration of the above-identified patent application as amended herein is respectfully requested. Claims 31-71 are pending in the subject application and have been examined on the merits.

In the Office Action, claims 31-71 have been rejected under 35 U.S.C. § 112, ¶ 1, as purportedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. In other words, claims 31-71 have been rejected as purportedly failing to comply with the enablement requirement.

The Office Action also included the following grounds for rejection:

(a) Claims 31-32, 36-38, 48-49, 53-56, 61-66 and 68-70 were rejected under 35 U.S.C. § 102(e) as anticipated by Lam et al. (US Patent No. 6,733,530, hereinafter "Lam");

(b) Claims 33-35, 39-47, 50-52, 57-60, 67 and 71 were rejected under 35 U.S.C. § 103(a) as obvious over Lam and further in view of Naughton et al. (US Patent No. 5,266,480, hereinafter "Naughton").

Applicants respectfully traverse these rejections. For the reason set forth below, it is believed that the claims are enabling, that Lam is not prior art for Applicants' claims and that Naughton does not render obvious claims 33-35, 39-47, 50-52, 57-60, 67 and 71.

The presently claimed invention is directed to a cultured skin construct having at least two layers, wherein the first layer is constituted by cultured dermal fibroblast cells that synthesize, assemble and produce a layer of extracellular matrix in the absence of any exogenous matrix components and/or a mesh member acting as a support during the culturing conditions.

The second layer of cells is constituted by epithelial cells and it is disposed on the first layer to form an epidermal cell layer when the selected epithelial cells are keratinocytes. (*e.g.*, claims 31, 37, 39, 40, 48, 50-52 and 65-71, specification page 1, lines 20-29 to page 2, lines 1-6).

Claims 31-71 Satisfy 35 U.S.C.§ 112, ¶ 1

As an initial matter, Applicants note that Supervisor Examiner Jeffrey Fredman during the interview of January 27, 2005 held with Applicants' representatives Edward Adamson, Esq. and Alison Corkery, Esq. agreed to withdraw this very exact enablement rejection under 35 U.S.C. §112, ¶ 1. And thus, Applicants respectfully request that this rejection be withdrawn as agreed.

Nevertheless, in the interest of completing the record for appeal purposes, Applicants again provide the following response to address this rejection. First, it appears that the *Office Action* erroneously requires that the Specification disclose "any and all culture conditions" that would lead to the formation of the claimed skin construct. *Office Action*, p. 4. This is clearly not a proper application of the enablement requirement under 35 U.S.C. § 112, ¶ 1.

Rather, the enablement requirement is that the specification must teach one of ordinary skilled in the art how to practice the claimed invention without undue experimentation. *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916); *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In fact, the teaching of a single embodiment may be sufficient to satisfy the enablement requirement under 35 U.S.C. § 112, ¶1 so long as one of ordinary skill in the art may practice the claimed invention without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Circ. 1988).

Thus, Applicants first submit that the *Office Action*'s application of the enablement requirement is incorrect and for that reason, the rejection should be withdrawn.

Additionally, the Office Action also appears to incorrectly assert that the claims are not enabled because the claims themselves "fail to recite what are the culturing conditions..." *Office Action,* pp. 5-6. As the Examiner is well aware, the proper question for enablement is whether the specification teaches one of ordinary skill in the art how to practice the claimed invention without undue experimentation, not whether the claims themselves include those process conditions. *Telectronics, Inc.,* 857 F.2d at 785, 8 USPQ2d at 1223. As such, for this additional reason of incorrectly applying the enablement requirement to what is recited in the claims, Applicants respectfully request withdrawal of this rejection.

As explained above, Applicants respectfully submit that the proper inquiry for performing an enablement analysis under 35 U.S.C. § 112, ¶ 1 is: does the specification, coupled with information known in the art, teach one of ordinary skill in the art how to practice the claimed invention without undue experimentation? And Applicants respectfully submit that the answer is yes. In fact, the *Office Action* at page 4 admits that the Specification teaches optimization of culture conditions for human fibroblasts to produce a layer of extracellular matrix in the absence of exogenous matrix components (*e.g.*, Examples 1, 3, 15). Therefore, it necessarily follows that the Specification is enabling for practicing the claimed invention (*e.g.*, Specification p. 7, lines 4-19; p. 9, line 1 to p. 10, line 20; p. 11, line 11 to p. 18, line 26; p. 19 line 7 to p. 20 line 11; Examples 1, 3, 5, 6, 9, 10, 15, 17 and figure 1).

In addition to this admission from the *Office Action*, an analysis of the *Wands* factors confirms that one of ordinary skill in the art would indeed be able to practice the claimed invention without undue experimentation. That is, one of ordinary skill in the art would be able to, from reading the Specification, prepare without undue experimentation a cultured skin

construct with at least two layers comprising cultured fibroblasts which synthesize, assemble and produce a layer of extracellular matrix in the absence of both exogenous matrix components and a mesh member during the culturing conditions, and at least a second layer of keratinocytes cells disposed on the first cell layer to form an epidermal cell layer. *Faria Declaration*, ¶ 10.

A review of the eight (8) *Wands* factors is presented below:

1. Breadth of the claims

Claims 31-71 are directed to cultured skin constructs having at least two layers of cells, comprising a first layer of fibroblast cells producing an extracellular matrix layer in the absence of both exogenous matrix components and a mesh member during the culturing conditions and a second layer of epithelial cells disposed on the first cell layer. The second layer may form an epidermal cell layer when the selected epithelial cells are keratinocytes. There may also be a third layer of cells disposed on the second layer. The claims also include methods of making and using the skin construct.

2. Nature Of The Invention

The claimed invention is directed to a cultured skin construct and to a method for preparing or using it. The nature of the invention is in the field of tissue engineering, or more specifically, the technology relates to the preparation of tissue constructs.

3. The State Of The Prior Art

The art of culturing dermal fibroblast cells that produce collagen and extracellular matrix is well known in the art. *Faria Declaration*, ¶ 11. For example, as cited by the Examiner, the art U.S. Patent No. 6,733,530

(Lam) describes how to prepare a layer of cultured dermal fibroblast cells which produces a number of proteins such as native collagen fibers and fibronectin.

It is also well known in the art that dermal fibroblast cells naturally produce type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans, among other byproducts. *Faria Declaration*, ¶ 11; (*e.g.*, Specification, page 3, lines 19-23, page 4, line 1, to page 5 line 2, page 5 line 26, to page 6 line 5, page 7 lines 20-27, page 8, lines 20-29, etc.). This is confirmed by the Examiner's own asserted art. *E.g.*, U.S. Patent No. 5,266,480 (Naughton), col. 13, lines 65-67.

It is also well known in the art how to form an epidermal cell layer from keratinocyte cells, which are naturally found in such epidermal cell layers. *Faria Declaration*, ¶ 12; (*e.g.*, Specification page 19, lines 18-22, citing U.S. Patent Nos. 5,712,163 and 5,536,656 and page 21, lines 5-6 citing U.S. Patent No. 5,374,515).

It is further well known what culture media may be used to grow a layer of dermal fibroblasts or epidermal cell layer to produce their natural byproducts. *Faria Declaration*, ¶ 13; (*e.g.*, Specification, page 11, line 25, to page 12 line 12, page 12, lines 13-28. The Specification even incorporates by reference a number of references teaching such culture media (*e.g.*, Specification, page 12, line 29 to page 13 line 9).

However, the state of the prior art was such that any such tissue construct must include exogenous matrix components and mesh member to support the construct. *Faria Declaration*, ¶ 14 (*e.g.*, Specification, page

10, lines 21-29). For example, U.S. Patent Nos. 5,580,781, 5,443,950, 5,266,480, 5,032,508, 4,963,489, etc. all confirm the reliance on synthetic or mesh members for producing the tissue construct. *Faria Declaration*, ¶ 14. The *Office Action* acknowledges this point. *Office Action*, p. 4. There was nothing in the state of the art that taught, disclosed or even suggested that such a tissue construct could be prepared without such external mesh member. *Faria Declaration*, ¶ 14.

4. The Level Of One Of Ordinary Skill

One of ordinary skill in the art would be a scientist with an undergraduate degree in cell biology and at least two years of post graduate research or work experience in the field of tissue constructs. As such, one of ordinary skill in the art in view of the disclosure of the invention in the instant Specification would know how to prepare a layer of dermal fibroblast cells that produce an extracellular matrix having such natural byproducts such as type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans, etc. *Faria Declaration*, ¶ 9. One of ordinary skill in the art would further know which culture media may be used to prepare such layer. *Faria Declaration*, ¶ 9.

5. The Level Of Predictability In The Art

As stated above, it is well known what culture media may be used to grow a layer of dermal fibroblasts or epidermal cell layer to produce their natural byproducts. *Supra*, Wand Factor 3. It is also well known what culture media may be used to obtain those layers. *Id.* As such, the

state of the art is predictable in the preparation of those layers. *Faria Declaration*, ¶¶ 11-13.

6. The Amount Of Direction Provided

The present Specification provides a number of directions on how to prepare the tissue construct of the invention. For example, the Specification discloses the conditions to grow fibroblast cells (*e.g.*, Specification page 11, line 11, to page 14 line 8, page 14, line 16, to page 16 line 19 and Examples 1, 3, 5, 6, 9-11, 15, 17). *Faria Declaration,*¶ 16.

The Specification also discloses how to prepare a layer of extracellular matrix from dermal fibroblast cells in the absence of exogenous matrix components. (*e.g.*, Specification, page 17, lines 7-28, page 18, line 7, to page 19 line 6, page 23, line 26, to page 24 line 6, Example 1, 3, 5, 6, 9-11, 15, 17 and figure 1), *Faria Declaration*, ¶ 17. That is, the dermal fibroblast cells are permitted to grow until it obtains confluence, after which the cells then naturally produce the claimed byproducts which enable them to form a layer of extracellular matrix without the use of a synthetic mesh member. (*e.g.*, Specification, page 17, lines 7-9), *Faria Declaration*, ¶ 17.

The Specification further teaches how to prepare a layer of epidermal cells. (*e.g.*, Specification, page 5, lines 8-25, page 19, lines 7-25; page 20, line 12, to page 21 line 11, page 21, line 26, to page 23 line 2, Examples 2, 8, 12 and 16. *Faria Declaration*, ¶ 18. That is, the layer of epidermal cells are grown by seeding and culturing epithelial cells to the

upwardly facing surface of the cell-matrix construct to form a multilayer cell construct (*e.g.*, Example 2).

The Specification discloses the conditions to grow epidermal cells, including induction of differentiation and cornification to form a differentiated keratinocyte layer (*e.g.*, page 19, lines 18-25, citing U.S. Patent Nos. 5,712,163 and 5,536,656). Thus, the Specification is enabling for both, the optimization of culture conditions for human fibroblasts to produce a layer of extracellular matrix in the absence of exogenous matrix components (*e.g.*, page 17, lines 7-24, page 18, 7-19, Examples 1, 3, 5, 6, 9, 10, 15, 17 and figure 1), and for growing epidermal cells (*e.g.*, page 19, lines 18-25, citing U.S. Patent Nos. 5,712,163 and 5,536,656).

As set forth above, the Specification provides ample guidance for practicing the claimed invention. *Faria Declaration*, ¶ 19.

7. The Existence Of Working Examples

The Specification provides a number of working examples to practice the claimed invention. The working examples include a variety of different culturing conditions which can be used (*e.g.*, Examples 1, 2, 3, 5, 6, 8, 9, 10, 12, 15, 16, and 17).

8. The Quantity Of Experimentation Needed

The quantity of experimentation needed, if any, would not be undue. First, one of ordinary skill in the art with the prerequisite education and work experience would know how to practice the cell culture conditions for which the state of technology is well known in the art. (Factors 3-5, *supra*). Second, the Specification discloses how to

prepare a layer of extracellular matrix from dermal fibroblast cells in the absence of exogenous matrix components (Factor 6, *supra*). Third, the present Specification both discloses and further provides working examples of culturing human fibroblasts and formation of an epidermal layer. (Factors 6-7, *supra*). Therefore, for all of these reasons, one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. *Faria Declaration*, ¶¶ 20-21.

As such, for the reason set forth above, Applicants respectfully submit that since the present Specification provides a number of working examples, the Specification is enabling for the pending claims and request that the rejection of claims 31-71 under 35 U.S.C. § 112, ¶ 1 be reconsidered and withdrawn.

The Examiner's Wand Factor Analysis and Arguments Are Incorrect

In addition to the incorrect application of the enablement requirement as discussed *supra* at pages 3-4, the following analysis/arguments by the Examiner are also incorrect and merit the withdrawal of this rejection.

For example, in the State of Art and Predictability factor, the Examiner argues that "even though fewer than five engineered tissues have been approved, there are still many technical challenges to overcome before an "off-the-shelf" tissue could be created that represent the translation of scientific discoveries into treatments of patients. Furthermore, the successful large-scale production of tissue-engineered tissues requires an adequate source of healthy expandable cells, the optimization of the scaffolds, and the creation of bioreactors, which mimic the environment of the body and are amenable to scale-up. Additional challenges include the preservation of the product so that it has a long shelf-life and the successful use of various approaches to prevent tissue rejection." (*e.g.*, *Office Action*, page 5).

However, the claims of the present application are directed to cultured skin constructs having at least two layers comprising a first layer of cultured dermal fibroblast cells which produce, synthesize and assemble an extracellular matrix layer in the absence of both exogenous matrix components and a mesh member, and a second layer of epithelial cells, and not to what set forth at page 5 of the *Office Action*. Once again, Applicants submit that the *Office Action*'s application of the enablement requirement is incorrect and for that reason, the rejection should be withdrawn.

The *Office Action* again appears to incorrectly assert that the claims are not enabled because the claims themselves "fail to recite what are the culturing conditions..." This erroneous standard is also applied in the "Response to Arguments" section of the *Office Action*, at page 6 (*e.g.*, "similarly, the instant claims fail to recite..."). As set forth above at pages 3-4, the enablement requirement is that the Specification must teach one of ordinary skill in the art how to practice the claimed invention without undue experimentation, *Mineral Separation v. Hyde*, 242 U.S. at 270 (1916); *In re Wands*, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), not whether the claims themselves include those process conditions. *Telectronics, Inc.*, 857 F.2d at 785, 8 USPQ2d at 1223. As such, for incorrectly applying the enablement requirement to what is recited in the claims, Applicants respectfully request withdrawal of this rejection.

In addition, the *Office Action* argument that the assembly of the cells into tissue is a highly orchestrated series of events does not render the present Specification non-enabling for practicing the invention because, as explained *supra* at pages 8-9 the Specification teaches one skilled in the art how to practice the claimed invention without undue experimentation.

Finally, the *Office Action* at page 7 acknowledges that the Specification discloses various chemically defined media like growth medium, production medium, etc, but that it is

unclear which media is used at each step during the development of the cultured skin construct as claimed. On the contrary, it is disclosed by the Specification and it is well within the knowledge of one skilled in the art which media to use at each step during the development of the cultured skin construct without undue experimentation. *Faria Declaration*, ¶¶ 20-21.

As such, for all the reasons set forth above, Applicants respectfully submit that the Specification is enabling for the pending claims and request that the rejections of claims 31-71 under 35 U.S.C. § 112, ¶ 1 be reconsidered and withdrawn.

A. The Reference Is Not Prior Art for Applicants' Claim

In the Office Action, claims 31-32, 36-38, 48-49, 53-56, 61-66 and 68-70 were rejected under 35 U.S.C. § 102(e) as anticipated by Lam.

A reference can only be used as a 35 U.S.C. § 102(e) reference if its filing date precedes the effective filing date of the claims to which the rejection is applied to. The effective filing date of the pending claims is November 19, 1998, the filing date of the provisional application U.S.S.N. 60/109,247 which fully supports the claimed subject matter.

On the other hand, Lam's filing date is August 2, 1999, which is well after Applicants' November 19, 1998 effective filing date. As such, Lam is not prior art to Applicants' claims and withdrawal of the rejection of the claims under 35 U.S.C. § 102(e) as anticipated by Lam is respectfully requested.

B. The Cited Prior Art Does Not Render Obvious Applicants' Claims

As set forth in the preceding section, Lam cannot be used an anticipatory reference under 35 U.S.C. § 102(e). Thus, Lam cannot be used to support a rejection under 35 U.S.C. § 103. *Ex parte Andresen*, 212 USPQ 100, 102 (Bd. Pat. App. & Inter. 1981).

Naughton teaches and discloses a three dimensional cell culture system wherein the cells are derived from a desired tissue and are inoculated and grown on a stromal support

matrix made of nylon, Dacron, polystyrene, polypropylene, polyacrylates, polyvinyl compounds, polycarbonate, polytetrafluorethylene, thermanox, nitrocellulose, cotton, polyglycolic acid, cat gut sutures, gelatin, dextran, etc. Any of these materials may be woven into a mesh, for example, to form the three-dimensional matrix (*e.g.*, col. 5, lines 13-18, col. 10 lines 65-68 to col. 11, lines 1-7).

Thus, Naughton does not teach or suggest the presently claimed invention (*e.g.*, claims 31, 37, 39, 48, 65, 66, 68, 69, 70 and 71) and does not render obvious claims 31-32, 36-38, 48-49, 53-56, 61-66 and 68-70. Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) is respectfully requested.

D. Conclusion

In light of the foregoing, the application is now believed to be in proper condition for allowance and a Notice to that effect is respectfully requested. If this *Amendment and Response* does not otherwise result in the issue of such Notice, the Examiner is respectfully invited to contact the Applicants' undersigned counsel for an interview.

No extra fee is believed due. However, if any additional fees are necessary, the Director is hereby authorized to charge such fees to Deposit Account No. 50-0540.

Furthermore, Applicants are not aware of any prior art that has all of the elements of the claim or which in proper combination with other prior art would provide all of the elements of the claim.

Respectfully submitted,

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